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Prediction of Adverse Pregnancy Outcomes in Women with Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease associated with major obstetrical complications such as gestational loss, preterm delivery, fetal growth restriction (FGR) and preeclampsia. Published literature is not consensual regarding the main risk factors for each of these outcomes. Our goal with this study was to determine the most important predictors for each of the main adverse pregnancy outcomes in this population. We conducted a retrospective cohort study of unifetal pregnancies of women with the diagnosis of SLE followed in our unit between January 1994 and December 2016. We excluded elective terminations of pregnancy and cases lost to follow-up and we analyzed 157 pregnancies (128 women). Multiple logistic regression models for the outcomes gestational loss, preterm delivery, fetal growth restriction, and preeclampsia were built. Two-sided p-values of < 0.05 were used to determine statistical significance, and two-sided confidence intervals of 95% are reported. In our cohort, the main risk factors for gestational loss were maternal age and the presence of antiphospholipid antibodies. Lupic nephritis was predictive of a preterm delivery and preeclampsia. Renal involvement and lupus flares during pregnancy were risk factors for FGR. Overall, the main risk factor for an adverse pregnancy outcome were lupus flares during pregnancy. Despite optimal pregnancy monitoring, women with SLE are still at risk for adverse pregnancy outcomes. Risk stratification for each of these outcomes is crucial for an effective counselling and tailored monitoring.

Keywords Systemic lupus erythematosus · Pregnancy · Gestational loss · Fetal growth restriction · Preeclampsia · Preterm birth

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease that can affect every organ and system and usually follows a relapsing and remitting course. Its prevalence is estimated around 23.2 cases per 100.000 person-years in North America. Its incidence is globally rising, possibly due to the increased awareness for the disease and improvement of diagnostic tools that allow the detection of milder presentations of SLE [1]. Females have a higher incidence of SLE when compared with men, with a sex ratio ranging from 2:1 to 15:1 [1]. In fact, this condition frequently affects women of childbearing age, suggesting a role for hormonal factors in the pathogenesis of the disease [2, 3].

SLE has been associated with major maternal, obstetrical, and neonatal complications. Exacerbation of the disease, gestational loss, preterm delivery, fetal growth restriction (FGR), preeclampsia, and HELLP syndrome have been described in pregnant or puerperal SLE patients, and neonatal lupus has been reported in their offspring [2, 4–6].

Most studies show that the prognosis for the pregnancy is globally worse when there is renal involvement (often in the setting of positive antiphospholipid antibodies), although there appear to be different clinical and laboratorial predictors for each of the individual adverse pregnancy outcomes [6]. The knowledge of these risk factors is crucial for an effective counselling and tailoring of fetal and maternal monitoring in this population.

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Previous studies are not consensual on the predictors for each of the adverse pregnancy outcomes [4, 7, 8] and some fail to account for other important risk factors. Our goal with this study was to determine the key risk factors for each of the main obstetric adverse pregnancy outcomes in women with SLE in our cohort.

Patients and Methods

Patient Selection

We conducted a retrospective cohort study of unifetal pregnancies of women with the diagnosis of SLE followed in our obstetric unit of autoimmune diseases between January 1994 and December 2016. All patients with positive antiphospholipid antibodies were medicated with aspirin and low molecular weight heparin according to our unit's guidelines.

From an initial population of 189 pregnancies, we excluded multiple pregnancies ($n = 4$), elective termination of pregnancy before 11 weeks ($n = 12$) and cases lost to follow-up ($n = 16$) and we analyzed the outcomes of 157 pregnancies (corresponding to 128 women) (Fig. 1).

Clinical Data

Clinical, laboratory, and sonographic data was collected from individual patient charts.

Definitions

The diagnosis of SLE was confirmed in the patient's medical records and classified in terms of target organ affection according to the patient history and laboratory data. The date of diagnosis and presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and beta-2-glycoprotein I) were also obtained through medical records. The patients were considered to be positive for antiphospholipid antibodies if at least one of them was present on two or more occasions 12 weeks apart. Anticardiolipin antibodies (IgG and IgM) were identified with an enzyme-linked immunosorbent assay (ELISA) [9]. Beta-2-glycoprotein I antibodies were not routinely measured until 2006, and from that date forward they were identified with ELISA. Lupus anticoagulant was assessed by multiple coagulation tests using platelet-poor plasma samples, following internationally accepted guidelines [10].

A lupus flare was defined as a significant worsening of clinical symptoms or laboratorial measurements. The disease was considered active in the moment of conception if the last flare was less than 6 months before the diagnosis of pregnancy.

Gestational loss was defined as either first trimester spontaneous abortion or fetal death. Births before 37 weeks of gestation were classified as preterm. Fetal growth restriction was diagnosed when estimated fetal weight was below the 10th centile for a given gestational age, associated with Doppler abnormalities. Preeclampsia was defined as a new-onset persistent hypertension (blood pressure > 140/90 mmHg) after 20 weeks of gestation in association with new-onset proteinuria (300 mg or more of protein in a 24-h urine collection) or hypertension without proteinuria but associated with organ dysfunction: thrombocytopenia, liver damage, new development of renal failure, pulmonary edema, or new-onset cerebral or visual complaints. HELLP syndrome was diagnosed in the presence of laboratorial signs of hemolysis, elevated enzyme levels, and low platelet levels. A composite adverse outcome was defined as the presence of one or more of the following: gestational loss, preterm delivery, preeclampsia, HELLP syndrome, fetal growth restriction, or neonatal death.

Statistical Analysis

Continuous data were reported as means and standard deviations. Categorical data were reported as numbers and proportions. Proportions were compared using the chi-square test or Fisher's exact test, and means were compared using Student's *t* test. Multiple logistic regression models were used to analyze the binary outcomes (gestational loss, preterm delivery, fetal growth restriction, and preeclampsia) controlling for confounders. Confounders were selected based on previous literature, tested and remained in the model based on statistical significance. Two-sided *p*-values of < 0.05 are used to determine statistical significance, and two-sided confidence intervals of 95% are reported.

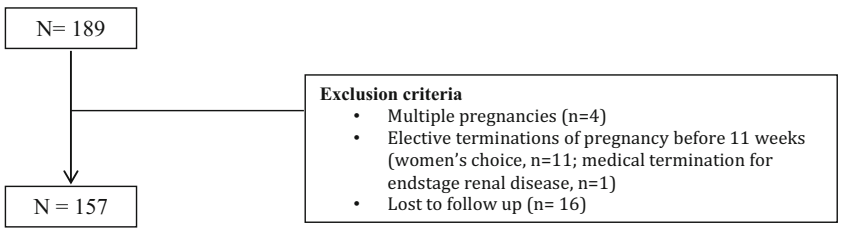

Fig. 1 Patient selection

Results

The characteristics of our population are summarized in Table 1. Mean maternal age is 29.6 years, and the majority of women are nulliparas (61%). The prevalence of chronic hypertension in our cohort is 14%. Regarding obstetric history, 10.2% of women have had a previous preterm birth. The history of any previous gestational loss is remarkable (43%), the majority of which on the first trimester (23.1%) but more 10% of women report a history of at least one second trimester loss.

Regarding SLE, the mean time of disease evolution is 6.8 years (SD 5.4). Approximately 32% of patients have renal involvement and 25.5% have at least one positive antiphospholipid antibody. Lupus anticoagulant is positive in 12.1% of patients and around 23% have SSA or SSB antibodies. The majority of patients did not have an active disease in the moment of conception (90.7%). Lupus flares during pregnancy were reported in 15 gestations (9.6%).

Concerning the outcomes of pregnancy, mean gestational age at delivery was 37 weeks (SD 2.3) with a mean neonatal birthweight of 2808.3 g (SD 617). Nine women had a gestational loss (5.7%). Roughly one-quarter of the population had a preterm delivery (24.3%). Preeclampsia complicated 11 pregnancies (7.2%) and we had one case of HELLP syndrome (0.66%). Fetal growth restriction was diagnosed in 13.2% of pregnancies. There was one neonatal death (0.66%). The overall occurrence of an adverse pregnancy outcome was 38.9%.

Table 1 Description of the population

	N = 157
Maternal characteristics	
Maternal age (years), mean (SD)	29.6 (4.7)
Nulliparity	96 (61.1%)
Chronic hypertension	22 (14%)
History of fetal growth restriction	2 (1.3%)
History of preeclampsia	2 (1.3%)
History of preterm delivery	16 (10.2%)
History gestational loss	68 (43.3%)
First trimester	1–3 losses: *n* = 35 (22.4%; > 3 losses: 1 (0.64%)
Second trimester	1–3 losses: *n* = 17 (10.8%)
Third trimester	1 loss: *n* = 2 (1.3%)
Lupus characteristics	
Time from diagnosis (years), mean (SD)	6.8 (5.4)
Renal involvement	49 (31.6%)
Active disease in the moment of conception	14 (9.3%)
Presence of one or more antiphospholipid antibodies	40 (25.5%)
Presence of lupus anticoagulant	19 (12.1%)
Presence of anti-SSA or anti-SSB	36 (22.9%)
Lupus flare during pregnancy	15 (9.6%)
Pregnancy outcome	
Mean gestation; age at delivery (weeks), mean (SD)	36.9 (2.3%)
Preterm birth	36 (24.3%)
Gestational loss	9 (5.7%)
Preeclampsia	11 (7.2%)
HELLP syndrome	1 (0.66%)
Fetal growth restriction	20 (13.2%)
Type of delivery	
Vaginal	86 (58.1%)
Caesarean	62 (41.9%)
Birth weight (g), mean (SD)	2808.3 (617)
Neonatal death	1 (0.67%)
Composite adverse pregnancy outcome	61 (38.9%)

Values correspond to number of observations-*n*, and percentage of population (), unless otherwise specified

Gestational Loss

In pregnancies complicated by gestational loss (Table 2), women were significantly older when compared with those without losses (33.7 vs 29.4 years, $p < 0.01$). They had a more frequent past history of preterm delivery (44.4% vs 8.1%, $p = 0.007$) and gestational loss, particularly in the second trimester (55.6% vs 8.1%, $p < 0.01$).

These patients had a higher mean time from the diagnosis of lupus (8.2 vs 6.4 years, $p < 0.01$) and were more frequently positive for one or more antiphospholipid antibodies (66.7% vs 23%, $p < 0.01$) (Table 2).

When testing the influence of time from diagnosis of lupus in gestational loss in a multiple logistic regression model, controlling for maternal age and number of previous gestational losses this association does not seem significant ($p = 0.14$) (Supplementary Table 1).

On the other hand, in a similar multiple logistic regression model, the presence of one or more antiphospholipid antibodies was positively correlated with the occurrence of gestational loss, even after controlling for maternal age and number of previous gestational losses, OR = 6.02 (95% CI 1.29; 28.13, $p = 0.02$).

In conclusion, the risk factors for gestational loss were maternal age, OR = 1.20 (95% CI 1.01; 1.42) and the presence of antiphospholipid antibodies, OR = 6.02 (95% CI 1.29; 28.13) (Supplementary Table 2).

Preterm Birth

Women that gave birth before 37 weeks of gestation (Table 3) were more frequently nullipara (83.3% vs 55.4%, $p < 0.01$) and had a higher prevalence of chronic hypertension (30.6% vs 8.9%, $p < 0.01$) and lupic nephritis (23.6% vs 58.3%, $p < 0.01$). Their pregnancies were more frequently complicated by lupus flares (25% vs 5.4%, $p < 0.01$).

When testing the association of lupic nephritis and lupus flares during pregnancy with preterm birth, in a multiple logistic regression model controlling for previous preterm birth, nulliparity and chronic hypertension, the presence of lupic nephritis is significantly correlated with the occurrence of preterm birth, OR = 4.06 (95% CI 1.63; 10.12, $p < 0.01$) while the incidence of lupus flares during pregnancy is marginally non-significant ($p = 0.06$) (Supplementary Table 3).

Therefore, the occurrence of preterm birth is significantly correlated only with lupic nephritis.

Fetal Growth Restriction

Women with growth restricted fetuses (Table 4) had a higher prevalence of lupic nephritis (55% vs 27.7%, $p = 0.02$) and active disease in the moment of conception

Table 2 Maternal characteristics according to gestational loss

	Gestational loss		
	No $n = 148$	Yes $n = 9$	p
Maternal characteristics			
Maternal age (years), mean (SD)	29.4 (4.49)	33.7 (6.12)	0.007*
Nulliparity	92 (62.2%)	4 (44.4%)	0.311
Chronic hypertension	21 (14.2%)	1 (11.1%)	0.633
History of fetal growth restriction	2 (1.35)	0 (0%)	0.88
History of preeclampsia	2 (1.35)	0 (0%)	0.88
History of preterm delivery	12 (8.1)	4 (44.4%)	0.007*
History of gestational loss			
First trimester	35 (23.6%)	1 (11%)	0.08
Second trimester	12 (8.1%)	5 (55.6%)	<0.001*
Third trimester	2 (1.3%)	0 (0%)	0.88
Lupus characteristics			
Time from diagnosis (years), mean (SD)	6.4 (5.01)	13 (8.21)	0.007*
Renal involvement	47 (32.2%)	2 (22.2%)	0.72
Active disease in the moment of conception	14 (10.5%)	0 (0%)	0.47
Presence of one or more antiphospholipid antibodies	34 (23%)	6 (66.7%)	0.009*
Presence of lupus anticoagulant	16 (10.8%)	3 (33.3%)	0.079
Presence of anti-SSA or anti-SSB	35 (23.7%)	1 (11.1%)	0.69
Lupus flare during pregnancy	15 (10.1%)	0 (0%)	0.60

Values correspond to number of observations - n, and percentage of population (), unless otherwise specified

Table 3 Maternal characteristics according to preterm delivery

	Preterm delivery		
	No $n = 112$	Yes $n = 36$	p
Maternal characteristics			
Maternal age (years), mean (SD)	29.7 (4.66)	28.3 (3.81)	0.12
Nulliparity	62 (55.4%)	30 (83.3%)	0.003*
Chronic hypertension	10 (8.9%)	11 (30.6%)	0.004*
History of fetal growth restriction	1(0.89%)	1(2.78%)	0.429
History of preeclampsia	2 (1.79%)	0 (0%)	0.571
History of preterm delivery	11(9.82%)	1(2.78%)	0.467
History of gestational loss			
First trimester	29 (25,89%)	6 (16,67%)	0.605
Second trimester	10 (8.93%)	2 (5.56%)	1.00
Third trimester	2 (1.79%)	0 (0%)	1.00
Lupus characteristics			
Time from diagnosis (years), mean (SD)	6.17 (5.16)	7.25 (4.50)	0.267
Renal involvement	26(23.64%)	21(58.33%)	< 0.001*
Active disease in the moment of conception	10 (9.9%)	4 (12.12%)	0.746
Presence of one or more antiphospholipid antibodies	26 (23.2%)	8 (22.2%)	1.00
Presence of lupus anticoagulant	13 (11.6%)	3 (8.33%)	0.762
Presence of anti-SSA or anti-SSB	30 (26.8%)	5 (13.9%)	0.175
Lupus flare during pregnancy	6 (5.4%)	9 (25%)	0.002*

Values correspond to number of observations - n, and percentage of population (), unless otherwise specified

(28.6% vs 8.2%, $p = 0.04$). Their pregnancies were more frequently complicated by lupus flares (35% vs 6%, $p < 0.01$).

When analyzing the association between fetal growth restriction (FGR) and lupic nephritis, active disease in the moment of conception and lupus flares during pregnancy, controlling for chronic hypertension, both renal involvement, OR = 5.60 (95% CI 1.23; 23.60, $p = 0.02$) and lupic flares during pregnancy, OR = 4.78 (95% CI 1.08; 21.08, $p = 0.04$) were significantly associated with the outcome. The presence of an active disease in the moment of conception was marginally non-significant ($p = 0.06$) (Supplementary Table 4).

In conclusion, renal involvement and lupus flares during pregnancy were risk factors for FGR.

Preeclampsia

In pregnancies complicated by preeclampsia (Table 5), women appear to be younger (25.3 vs 29.9 years, $p < 0.01$) and more frequently nulliparas (81.8% vs 59.6%, $p < 0.20$). These women have a higher prevalence of lupic nephritis (81.8% vs 27.3%, p < 0.01).

After controlling for maternal age, nulliparity and chronic hypertension in a logistic regression model, the positive association between lupic nephritis and preeclampsia remained, OR = 29.78 (95% CI 3.84; 281.11, $p < 0.01$) (Supplementary Table 5).

Composite Adverse Pregnancy Outcome

Women whose pregnancy was complicated by gestational loss, preterm delivery, preeclampsia, HELLP syndrome, fetal growth restriction, or neonatal death (Table 6) were more frequently nulliparas (73.8% vs 53.1%, $p = 0.01$). They had a higher prevalence of lupic nephritis (42.6% vs 24.5%, $p = 0.02$) and a higher incidence of lupus flares during pregnancy (19.7% vs 3.1%, $p < 0.01$).

After controlling for maternal age, chronic hypertension, nulliparity, number of previous gestational losses and history of prematurity, a strong positive association between lupus flares during pregnancy and the composite pregnancy outcome remained OR = 4.72 (95% CI 1.20; 18.63, $p = 0.03$) while the association between this outcome and lupic nephritis was not significant ($p = 0.11$) (Supplementary Table 6).

Discussion

Gestational loss (encompassing early pregnancy loss and fetal demise) is described in up to 22% of SLE patients [4].

Table 4 Maternal characteristics according to fetal growth restriction

	Fetal growth restriction		
	No *n* = 132	Yes *n* = 20	*p*
Maternal characteristics			
Maternal age (years), mean (SD)	29.80	27.75	0.068
Nulliparity	79 (59.9%)	14 (70%)	0.466
Chronic hypertension	17 (12.9%)	5 (25%)	0.172
History of fetal growth restriction	1 (0.76%)	1 (5%)	0.247
History of preeclampsia	1 (0.76%)	1 (5%)	0.247
History of preteen delivery	13 (9.9%)	3 (15%)	0.445
History of gestational loss			
First trimester	34 (25.8%)	2 (10%)	0.162
Second trimester	17 (12.9%)	0 (0%)	0.130
Third trimester	2 (1.5%)	0 (0%)	1.00
Lupus characteristics			
Time from diagnosis (years), mean (SD)	6.86 (5.68)	5.78 (2.82)	0.431
Renal involvement	36 (27.7%)	11 (55%)	0.020*
Active disease in the moment of conception	10 (8.2%)	4 (28.6%)	0.039*
Presence of one or more antiphospholipid antibodies	34 (25.8%)	4 (20%)	0.783
Presence of lupus anticoagulant	16 (12.1%)	1 (5%)	0.701
Presence of anti-SSA or anti-SSB	32 (24.2%)	4 (20%)	0.785
Lupus flare during pregnancy	8 (6.0%)	7 (35%)	0.001*

Values correspond to number of observations - *n*, and percentage of population (), unless otherwise specified

Table 5 Maternal characteristics according to preeclampsia

	Preeclampsia		
	No *n* = 141	Yes *n* = 11	*p*
Maternal characteristics			
Maternal age (years), mean (SD)	29.9 (4.67)	25.3 (2.61)	0.0016*
Nulliparity	84 (59.6%)	9 (81.8%)	0.204
Chronic hypertension	19 (13.5%)	3 (27.3%)	0.200
History of fetal growth restriction	2 (1.42%)	0 (0%)	1.00
History of preeclampsia	2 (1.42%)	0 (0%)	1.00
History of preterm delivery	16 (11.4%)	0 (0%)	0.607
History of gestational loss			
First trimester	34 (24.8%)	1 (9.1%)	0.460
Second trimester	16 (11.4%)	1 (9.1%)	1.00
Third trimester	2 (1.4%)	0 (0%)	1.00
Lupus characteristics			
Time from diagnosis (years), mean (SD)	6.7 (5.6)	7.4 (3.4)	0.643
Renal involvement	38 (27.3%)	9 (81.8%)	0.001*
Active disease in the moment of conception	12 (9.5%)	2 (20%)	0.274
Presence of one or more antiphospholipid antibodies	35 (24.8%)	3 (27.3%)	1.00
Presence of lupus anticoagulant	1702.1%)	0 (0%)	0.613
Presence of anti-SSA or anti-SSB	34 (24.1%)	2 (18.2%)	1.00
Lupus flare during pregnancy	14 (9.9)	1 (9.1)	1.00

Values correspond to number of observations - n, and percentage of population (), unless otherwise specified

Table 6 Maternal characteristics according to composite adverse pregnancy outcome

	Composite adverse pregnancy outcome		
	No $n = 96$	Yes $n = 61$	p
Maternal characteristics			
Maternal age (years), mean (SD)	29.9 (4.9)	29.1 (4.4)	0.297
Nulliparity	51 (53.1%)	45 (73.8%)	0.012*
Chronic hypertension	9 (9.4%)	13 (21.3%)	0.057
History of fetal growth restriction	1 (1.0%)	1 (1.6%)	1.00
History of preeclampsia	1(1.0%)	1(1.6%)	1.00
History of preterm delivery	9 (9.4%)	7 (11.5%)	0.788
History of gestational loss			
First trimester	26(27.1%)	10(16.4%)	0.172
Second trimester	8 (8.3%)	9 (14.8%)	0.292
Third trimester	2(2.1%)	0 (0%)	0.522
Lupus characteristics			
Time from diagnosis (years), mean (SD)	6.3 (5.4)	7.6 (5.3)	0.159
Renal involvement	23 (24.5%)	26 (42.6%)	0.022*
Active disease in the moment of conception	8 (9.0%)	6 (11.5%)	0.771
Presence of one or more antiphospholipid antibodies	20 (20.8%)	20 (32.8%)	0.132
Presence of lupus anticoagulant	10 (10.4%)	9 (14.8%)	0.457
Presence of anti-SSA or anti-SSB	26 (27.1%)	10 (16.4%)	0.172
Lupus flare during pregnancy	3 (3.1%)	12 (19.7%)	0.001*

Values correspond to number of observations - n, and percentage of population (), unless otherwise specified

Some studies identify the presence of antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant and beta-2-glycoprotein I antibodies) as the main determinants for this outcome, particularly if there is multiple positivity or positivity for lupus anticoagulant [5] although there are some conflicting results [11]. Lupus activity in the moment of conception and disease flares were also suggested as important risk factors for this outcome [7, 12]. Moreover, the presence of SSA/Ro or SSB/La antibodies is a known cause of fetal complete atrioventricular heart block and fetal demise, particularly in the third trimester [5]. In our cohort, the overall incidence of gestational loss was much lower than expected (5.7%). We can hypothesize that differential loss to follow-up (16 cases) and scheduling of the first pregnancy appointment for a gestational age after the occurrence of a miscarriage, might explain this finding, since these women frequently choose to cancel their appointments after a pregnancy loss. The main risk factors for gestational loss were maternal age and the presence of one or more antiphospholipid antibodies, concordantly with previous studies. However, lupus activity in the moment of conception, disease flares during pregnancy and the presence of anti-SSA/SSB antibodies were not important risk factors after controlling for maternal age and number of previous gestational losses. We can hypothesize that this difference is due to the lack of adjustment for obstetric confounders in previous studies [7, 12]. We also cannot exclude that the small number of events ($n = 9$) compromises our power to detect a significant association.

The incidence of preterm birth is increased in women with SLE, with meta-analysis reporting rates as high as 34.9% [13]. In previous studies, the main predictor for this outcome appears to be lupus activity during pregnancy, with the preterm birth rate increasing two-thirds in women with mild-to-severe disease activity during pregnancy [8]. In our cohort, disease flares during gestation were a significant risk factor for preterm delivery in the univariate analysis. However, this association was not significant after controlling for the presence of lupus nephritis. On the other hand, renal involvement had a significant association with the outcome, both in the univariate analysis and in the multivariate model. In fact, the literature reports that lupus flares are more frequent when there is renal involvement [8] and in our cohort this seems to be the main driver for preterm delivery.

Fetal growth restriction is described in approximately 13% of pregnancies of women with SLE [14]. We found the exact same incidence in our cohort. Although its pathogenesis in the setting of SLE is not completely clear, the existence of

clinical/subclinical inflammation and the use of some medications during pregnancy were suggested as possible causal factors [15]. In our cohort, both renal involvement and lupus flares during pregnancy were significant risk factors for this outcome, which seems to highlight the role of inflammation in this pathway.

Preeclampsia rates are two-to-three fold increased in pregnancies with SLE [15]. This disorder has been associated with conditions that impair endothelial function, such as lupus nephritis [15]. Consistently with previous studies, in our cohort the presence of lupus nephritis was a significant risk factor for preeclampsia, after controlling for known confounders. Interestingly, a younger maternal age was also associated with an increased risk for preeclampsia in our cohort, contrary from the general population where older patients have a higher risk for this condition. We can hypothesize that in younger women there would be a higher prevalence of juvenile onset SLE, which is associated with worse outcomes [16]. However, we do not have the data in our records to test for that hypothesis.

Overall, the main risk factor for an adverse pregnancy outcome (gestational loss, preterm delivery, preeclampsia, HELLP syndrome, fetal growth restriction, or neonatal death) was the occurrence of lupus flares during pregnancy. This is consistent with previous reports [17] and highlights the importance of close monitoring of these pregnancies as well as the need to maintain adequate immunosuppression during this stage in order to minimize adverse outcomes.

Our study has some limitations inherent to a retrospective study design, namely the poor information regarding maternal medication use. The incidence of preeclampsia ($n = 11$) and gestational loss ($n = 9$) was low in our cohort, which decreases our power to detect significant associations with predictors, specifically in a multiple regression model. In addition, our cohort encompasses a vast period from 1994 to 2016. During this time frame, there were multiple advances in diagnostic criteria and medication use during pregnancy, changing the outcomes of the disease.

In conclusion, despite pregnancy monitoring in a specialized center, women with SLE are still considerably at risk for adverse pregnancy outcomes. This study provides a comprehensive analysis of the most important risk factors for the main adverse pregnancy outcomes after controlling for important confounders, which is often lacking in the literature. Overall, it can contribute to a better tailoring of obstetric surveillance of these pregnancies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that there are no conflicts of interest.

Ethical Approval This was a retrospective, observational study that in our institution did not require specific ethics approval.

Informed Consent This was a retrospective, observational study that in our institution, did not require specific informed consent.

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